

# Three aspects of an absolute configuration on the basis of the stereoisogram approach and revised terminology on related stereochemical concepts

Shinsaku Fujita

Received: 15 November 2013 / Accepted: 28 January 2014 / Published online: 7 February 2014  
© Springer International Publishing Switzerland 2014

**Abstract** A tetrahedral skeleton is considered to belong to the *RS*-stereoisomeric group denoted by  $\mathbf{T}_{d\sigma\hat{I}}$ . By placing proligands on the four positions of the tetrahedral skeleton, the resulting promolecule is considered to belong to a subgroup of  $\mathbf{T}_{d\sigma\hat{I}}$ , where its *RS*-stereoisomeric properties are illustrated by the corresponding stereoisogram. Three aspects of an absolute configuration, i.e., a chiral aspect, an *RS*-stereogenic aspect, and a scleral aspect, are formulated on the basis of three attributes of a stereoisogram, i.e., chirality, *RS*-stereogenicity, and sclerality. The *RS*-stereodescriptors of the Cahn-Ingold-Prelog (CIP) system are clarified to specify the *RS*-stereogenic aspect, so that they are assigned to a pair of *RS*-diastereomers contained in a type-I, type-III, or type-V stereoisogram. To apply the *RS*-stereodescriptors to the chiral aspect of an absolute configuration, the concept of *chirality faithfulness* is redefined by proposing *odd* and *even priority permutations*.

**Keywords** Absolute configuration · Stereoisogram · *RS*-Stereoisomeric group · Chirality faithfulness · *RS*-Stereodescriptor

## 1 Introduction

Terminology concerning *chirality center* and *absolute configuration* is suffering from serious confusion because of the lack of an appropriate mathematical framework.

1. In the glossary of the IUPAC Recommendations 1996 [1], the term *configuration* is defined as “In the context of stereochemistry, the term is restricted to the arrangement of atoms of a molecular entity in space that distinguishes *stereoisomers*, the

---

S. Fujita (✉)

Shonan Institute of Chemoinformatics and Mathematical Chemistry, Kaneko 479-7, Ooimachi, Ashigara-Kami-Gun, Kanagawa-Ken, 258-0019, Japan  
e-mail: shinsaku\_fujita@nifty.com

*isomerism* between which is not due to conformation differences. See also *absolute configuration* and *relative configuration*". And then the term *absolute configuration* is defined as "The spacial arrangement of the atoms of a chiral molecular entity (or group) and its stereochemical description, e.g., *R* or *S*."

2. On the other hand, the term *chirality center* is defined as "An atom holding a set of ligands in a spacial arrangement which is not superposable on its mirror image. A chirality center is thus a generalized extension of the concept of the *asymmetric carbon atom* to central atoms of any element, for example  $N^+abcd$ ,  $Pabcd$  as well as  $Cabcd$ ." in the IUPAC Recommendation 1996 [1].
3. Rule 91.1.1.1 of Provisional Recommendations 2004 [2] refers to the term *stereogenic unit* and points out the presence of three kinds of stereogenic units. Then, it states "... A chirality center, formerly known as an 'asymmetric atom', is the classical example of a stereogenic unit." and shows an example of assigning an *R*-descriptor to a chirality center of  $Xabcd$ .
4. Section 1.3 of [3] points out that the term *chirality element* is one of problematic terms: "This previously common term should be used with care. More appropriate is the term *stereogenic unit*". However, Table 1 of [3] maintains the usage of the terms *chirality center* ( $\subset$  *chirality units*) and '*pseudoasymmetric center*' ( $\subset$  '*pseudoasymmetric units*').
5. A representative textbook of stereochemistry [4, page 32] states "A chiral center (or, more properly, center of chirality) is a focus of chirality; in the case of carbon, at least, it corresponds to the asymmetric tetrahedral atom of van't Hoff as shown in Figure 3.7 ( $Cabcd$ )." The term *stereogenic centers* is used to designate a pair of Cl-substituted carbons in *cis*- and *trans*-1,3-dichlorocyclobutanes, where interchange of two ligands (Cl and H) at a stereogenic center leads to a stereoisomer. It is to be noted that the dichlorocyclobutanes are achiral. This means that stereogenic centers may be chiral or achiral.

A plausible interpretation may be summarized as follows:

"A chirality center is a kind of a stereogenic unit and its absolute configuration is characterized by *R* or *S*."

However, such *RS*-stereodescriptors are at the same time used to specify the absolute configurations of 'pseudoasymmetric centers', which are 'stereogenic centers', but not 'chirality centers'. Thus, the terminological change:

*asymmetric center*  $\rightarrow$  *chirality center*  
 $\rightarrow$  *chirality center* ( $\subset$  *stereogenic unit*)  $\rightarrow$  *stereogenic unit*

is not conceptually rationalized yet, because the situations itemized above are entangled.

To avoid such entangled situations, I have proposed the concepts of *RS*-*diastereomers* and *holantimers* in addition to *enantiomers*, which are integrated to give a quadruplet of *RS*-*stereoisomers* contained in a *stereoisogram* [5,6]. Such quadruplets of *RS*-*stereoisomers* are characterized by a new concept of *RS*-*stereoisomeric groups* [7–10]. They are categorized into five types on the basis of the factor groups of *RS*-*stereoisomeric groups* [11], because the factor groups are isomorphic to the Klein

four group having only five subgroups. A set of concepts *chirality*, *RS-stereogenicity*, and *sclerality* has been proposed on the basis of the stereoisogram approach, which stems from the mathematical framework based on *RS*-stereoisomeric groups. Thereby, the apparent inconsistency between geometrical features and *RS*-stereodescriptors is avoided in a succinct fashion [12–14].

Moreover, long-standing confusion on the term ‘prochirality’ in stereochemistry has been settled by the proposal of pro-*RS*-stereogenicity and integrated treatment with prochirality [15–17]. Thereby, *pro-R/pro-S*-descriptors are found to be specified by newly-defined *RS*-diastereotopic relationships, not by stereoheterotopic relationships used conventionally [18]. As a result, prochirality and pro-*RS*-stereogenicity based on the stereoisogram approach are clarified to be free from the conventional ‘prochirality’ and ‘prostereogenicity’ which suffer from serious confusion [19].

More recently, I have constructed an *RS*-stereoisomeric group denoted by  $\mathbf{T}_{d\bar{\sigma}\hat{\tau}}$  by starting from the point group  $\mathbf{T}_d$  for a tetrahedral skeleton. Such quadruplets as derived from the tetrahedral skeleton belong to subgroups of  $\mathbf{T}_{d\bar{\sigma}\hat{\tau}}$  and they are counted combinatorially on the basis of the unit-subduced-cycle-index (USCI) approach [20–22]. The combinatorial results [23, 24] can be used to rationalize the above-mentioned confused terminology in stereochemistry. Hence, the present article is devoted to integration and strict distinction between enantiomeric and *RS*-diastereomeric relationships. In particular, the confused terminology concerning chirality and absolute configuration will be discussed in detail from the viewpoint of combinatorial enumeration in the stereoisogram approach.

## 2 Quadruplets of *RS*-stereoisomers as equivalence classes

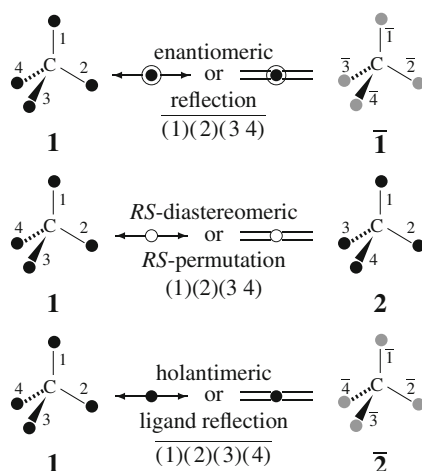
### 2.1 Pairs of enantiomers versus quadruplets of *RS*-stereoisomers

The conventional stereochemistry is based on the dichotomy between enantiomers and diastereomers, as found in textbooks on organic stereochemistry, although their expressions exhibit apparent differences: “Two stereoisomers cannot be at the same time both enantiomers and diastereomers of each other.” [25, page 51]; “By definition, any pair of stereoisomers which are not enantiomers of one another are called diastereomers.” [26, page 17]; “In this chapter (Chapter 3) we consider an alternative subdivision of stereoisomers: between enantiomers and diastereomers” [4, page 30]; and “The most concise definition, given in the plural, is ‘diastereoisomers are stereoisomers that are not enantiomers’.” [27, page 38].

From a mathematical point of view [28], enantiomeric relationships and stereoisomeric relationships serve as respective criteria for categorizing molecules into equivalence classes, while diastereomeric relationships are unable to generate equivalence classes.<sup>1</sup> The USCI (unit-subduced-cycle-index) approach [20] is based on enantiomeric relationships as equivalence classes, so that it counts each pair of enantiomers

<sup>1</sup> Suppose that a molecule is diastereomeric to a reference molecule. Then, another molecule enantiomeric to the former molecule is also diastereomeric to the reference molecule. This means that a set of diastereomeric molecules contains a pair of enantiomeric molecules.

**Fig. 1** Enantiomeric, *RS*-diastereomeric, and holantimeric relationships in a tetrahedral skeleton. A *solid circle* and a *half-tone solid circle* at a vertex represent a pair of enantiomeric ligands in isolation. They may coalesce to give an achiral ligand in isolation



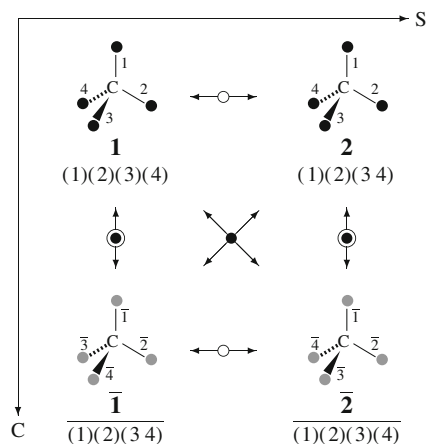
(or each achiral entity) once during combinatorial enumeration of tetrahedral entities under the point group  $T_d$ .

On the other hand, a quadruplet of *RS*-stereoisomers contained in a stereoisogram is an equivalence class, which is characterized by enantiomeric relationships, *RS*-diastereomeric relationships, and holantimeric relationships.

Let consider a tetrahedral skeleton **1**, where the four vertices are numbered sequentially (Fig. 1).

1. The reference promolecule **1** is converted into  $\bar{1}$  by means of a reflection operation, where the four substituents (proligands) represented by solid circles are converted into their counterparts with an opposite chirality sense (a half-tone solid circle). The pair of proligands may coalesce to give an achiral proligand in isolation. The resulting pair,  $1/\bar{1}$ , is in an enantiomeric relationship (if chiral) or in a self-enantiomeric relationship (if achiral).
2. The reference promolecule **1** is converted into **2** by means of an *RS*-permutation operation, where the four substituents (proligands) represented by solid circles maintain chirality sense in isolation. The resulting pair,  $1/2$ , is in an *RS*-diastereomeric relationship (if *RS*-stereogenic) or in a self-*RS*-diastereomeric relationship (if *RS*-stereogenic).
3. The reference promolecule **1** is converted into  $\bar{2}$  by means of a ligand-reflection operation, where the four substituents (proligands) represented by solid circles are converted into their counterparts with an opposite chirality sense (a half-tone solid circle). The pair of proligands may coalesce to give an achiral proligand in isolation. The resulting pair,  $1/\bar{2}$ , is in a holantimeric relationship (if scleral) or in a self-enantiomeric relationship (if scleral).

**Fig. 2** Stereoisogram concerning a quadruplet of **1**,  $\bar{1}$ , **2**, and  $\bar{2}$ . The double-headed arrows may be changed into equality symbols according to the five types of stereoisograms



## 2.2 Formulation of quadruplets of *RS*-stereoisomers

The promolecules appearing in Fig. 1, i.e., **1**,  $\bar{1}$ , **2**, and  $\bar{2}$ , construct a quadruplet of *RS*-stereoisomers, which is represented diagrammatically to generate a stereoisogram (Fig. 2) [5,6]. It should be noted that **2** (the *RS*-diastereomer of **1**) and  $\bar{2}$  (the holantimer of **1**) are enantiomeric to each other, that  $\bar{1}$  (the enantiomer of **1**) and  $\bar{2}$  (the holantimer of **1**) are *RS*-diastereomeric to each other, and that  $\bar{1}$  (the enantiomer of **1**) and **2** (the *RS*-diastereomer of **1**) are holantimeric to each other.

The quadruplet of *RS*-stereoisomers (**1**,  $\bar{1}$ , **2**, and  $\bar{2}$ ) and the corresponding stereoisogram is governed by an *RS*-stereoisomeric group  $\mathbf{T}_{d\bar{\sigma}\hat{\tau}}$ , which is an extension of the point group  $\mathbf{T}_d$ . The USCI (unit-subduced-cycle-index) approach has been extended to enumerate tetrahedral entities under the *RS*-stereoisomeric group  $\mathbf{T}_{d\bar{\sigma}\hat{\tau}}$ , where each quadruplet of *RS*-stereoisomers (Type I–V) is counted once [29]. The reference promolecule for such a quadruplet of *RS*-stereoisomers is fixed by a subgroup of  $\mathbf{T}_{d\bar{\sigma}\hat{\tau}}$ , just as the reference promolecule for a pair of enantiomers is fixed by a subgroup of  $\mathbf{T}_d$ .

The four vertices of a tetrahedral skeleton construct an orbit governed by the coset representation  $\mathbf{T}_{d\bar{\sigma}\hat{\tau}}/(\mathbf{C}_{3v\bar{\sigma}\hat{\tau}})$ , where the global symmetry  $\mathbf{T}_{d\bar{\sigma}\hat{\tau}}$  and the local symmetry  $\mathbf{C}_{3v\bar{\sigma}\hat{\tau}}$  characterize the behavior of the four vertices. To characterize the global and local symmetries of a derivative, subduction of  $\mathbf{T}_{d\bar{\sigma}\hat{\tau}}/(\mathbf{C}_{3v\bar{\sigma}\hat{\tau}})$  to each subgroup  $\hat{\mathbf{G}}_j$  ( $\subset \mathbf{T}_{d\bar{\sigma}\hat{\tau}}$ ) is listed in Table 1.

The four vertices of a tetrahedral skeleton accommodate a set of proligands so as to give a derivative, where the subduction listed in Table 1 decides the mode of packing of the proligands. Such a mode of packing is also characterized by the USCI-CF (the unit-subduced-cycle index with chirality fittingness). Under the action of  $\mathbf{T}_{d\bar{\sigma}\hat{\tau}}$ , each derivative is regarded as a representative of a quadruplet, belonging to a subgroup of  $\mathbf{T}_{d\bar{\sigma}\hat{\tau}}$ . Such representatives are listed in Fig. 3. Each compound number is attached by a partition  $[\theta]_i$  ( $i = 1-30$ ) to represent a constitution [23], e.g.,  $[\theta]_{10}$  ( $= [1, 1, 1, 1; 0, 0, 0, 0, 0, 0, 0, 0]$ ) attached to **3** for representing a constitution ABXY.

**Table 1** Subduction of  $T_{d\bar{\sigma}\hat{T}}/C_{3v\bar{\sigma}\hat{T}}$ 

	Subgroup ( $\downarrow \hat{G}_j$ )	Subduction ( $T_{d\bar{\sigma}\hat{T}}/C_{3v\bar{\sigma}\hat{T}} \downarrow \hat{G}_j$ )	USCI-CF	Type	Promolecules
1	$C_1$	$4C_1(/C_1)$	$b_1^4$	III	<b>20–25</b>
2	$C_2$	$2C_2(/C_1)$	$b_2^2$	III	
3	$C_{\bar{\sigma}}$	$C_{\bar{\sigma}}(/C_1) + 2C_{\bar{\sigma}}(/C_{\bar{\sigma}})$	$b_1^2 b_2$	II	<b>13–19</b>
4	$C_{\hat{\sigma}}$	$2C_{\hat{\sigma}}(/C_1)$	$c_2^2$	I	<b>4</b>
5	$C_s$	$C_s(/C_1) + 2C_s(/C_s)$	$a_1^2 c_2$	V	<b>32</b>
6	$C_{\hat{T}}$	$4C_{\hat{T}}(/C_{\hat{T}})$	$a_1^4$	I	<b>3</b>
7	$C_3$	$C_3(/C_1) + C_3(/C_3)$	$b_1 b_3$	III	
8	$S_{\bar{4}}$	$S_{\bar{4}}(/C_1)$	$b_4$	II	
9	$S_4$	$S_4(/C_1)$	$c_4$	V	
10	$D_2$	$D_2(/C_1)$	$b_4$	III	
11	$C_{2\bar{\sigma}}$	$C_{2\bar{\sigma}}(/C_{\bar{\sigma}}) + C_{2\bar{\sigma}}(/C'_{\bar{\sigma}})$	$b_2^2$	II	<b>10, 11</b>
12	$C_{2\hat{\sigma}}$	$C_{2\hat{\sigma}}(/C_1)$	$c_4$	I	
13	$C_{2v}$	$C_{2v}(/C_s) + C_{2v}(/C'_s)$	$a_2^2$	V	
14	$C_{s\bar{\sigma}\hat{\sigma}}$	$C_{s\bar{\sigma}\hat{\sigma}}(/C_{\bar{\sigma}}) + C_{s\bar{\sigma}\hat{\sigma}}(/C_s)$	$a_2 c_2$	IV	<b>31</b>
15	$C_{2\hat{T}}$	$2C_{2\hat{T}}(/C_{\hat{T}})$	$a_2^2$	I	
16	$C_{s\bar{\sigma}\hat{T}}$	$C_{s\bar{\sigma}\hat{T}}(/C_{\hat{T}}) + 2C_{s\bar{\sigma}\hat{T}}(/C_{s\bar{\sigma}\hat{T}})$	$a_1^2 a_2$	IV	<b>30</b>
17	$C_{3\bar{\sigma}}$	$C_{3\bar{\sigma}}(/C_{\bar{\sigma}}) + C_{3\bar{\sigma}}(/C_{3\bar{\sigma}})$	$b_1 b_3$	II	<b>6–9</b>
18	$C_{3v}$	$C_{3v}(/C_s) + C_{3v}(/C_{3v})$	$a_1 a_3$	V	
19	$C_{3\hat{T}}$	$C_{3\hat{T}}(/C_{\hat{T}}) + C_{3\hat{T}}(/C_{3\hat{T}})$	$a_1 a_3$	I	
20	$D_{2\bar{\sigma}}$	$D_{2\bar{\sigma}}(/C_{\bar{\sigma}})$	$b_4$	II	
21	$S_{\bar{4}\hat{\sigma}}$	$S_{\bar{4}\hat{\sigma}}(/C_s)$	$a_4$	IV	
22	$S_{\bar{4}\hat{T}}$	$S_{\bar{4}\hat{T}}(/C_{\hat{T}})$	$a_4$	IV	
23	$D_{2d}$	$D_{2d}(/C_s)$	$a_4$	V	
24	$S_{4\bar{\sigma}\hat{\sigma}}$	$S_{4\bar{\sigma}\hat{\sigma}}(/C_{\bar{\sigma}})$	$c_4$	IV	<b>29</b>
25	$D_{2\hat{T}}$	$D_{2\hat{T}}(/C_{\hat{T}})$	$a_4$	I	
26	$C_{2v\bar{\sigma}\hat{T}}$	$C_{2v\bar{\sigma}\hat{T}}(/C_{s\bar{\sigma}\hat{T}}) + C_{2v\bar{\sigma}\hat{T}}(/C'_{s\bar{\sigma}\hat{T}})$	$a_2^2$	IV	<b>28</b>
27	$T$	$T(/C_3)$	$b_4$	III	
28	$C_{3v\bar{\sigma}\hat{T}}$	$C_{3v\bar{\sigma}\hat{T}}(/C_{s\bar{\sigma}\hat{T}}) + C_{3v\bar{\sigma}\hat{T}}(/C_{3v\bar{\sigma}\hat{T}})$	$a_1 a_3$	IV	<b>27</b>
29	$D_{2d\bar{\sigma}\hat{T}}$	$D_{2d\bar{\sigma}\hat{T}}(/C_{s\bar{\sigma}\hat{T}})$	$a_4$	IV	
30	$T_{\bar{\sigma}}$	$T_{\bar{\sigma}}(/C_{3\bar{\sigma}})$	$b_4$	II	<b>5</b>
31	$T_{\hat{T}}$	$T_{\hat{T}}(/C_{3\hat{T}})$	$a_4$	I	
32	$T_d$	$T_d(/C_{3v})$	$a_4$	V	
33	$T_{d\bar{\sigma}\hat{T}}$	$T_{d\bar{\sigma}\hat{T}}(/C_{3v\bar{\sigma}\hat{T}})$	$a_4$	IV	<b>26</b>

## 2.3 Revised terminology

### 2.3.1 Absolute configuration

Organic stereochemistry is conventionally based on a single pair of attributes, i.e., chirality/achirality, as found in textbooks on stereochemistry [4, 25–27]. This stand-

point has resulted in an unconscious bias that the term *absolute configuration* is in connection with chirality only. Thereby, *RS*-stereodescriptors which specify absolute configurations have been linked directly to chirality in the original version of the Cahn-Ingold-Prelog (CIP) system [30]. Because this linkage has exposed conceptual difficulties [31], the term *stereogenicity* has been proposed in place of the term *chirality* to explain the basic principles of *RS*-stereodescriptors in the revision of the CIP system [3, 32]. However, this revision has provided an alternative confusion whether the term *absolute configuration* specified by the CIP system is concerned with chirality or with stereogenicity. This confusion cannot be avoided if we obey the conventional stereochemistry based on a single pair of attributes (chirality/achirality).

A stereoisogram (or a quadruplet of *RS*-stereoisomers) is characterized by three pairs of attributes: chirality/achirality, *RS*-stereogenicity/*RS*-astereogenicity, and sclerality/asclerality [5, 6]. The attribute *chirality* is concerned with enantiomeric relationships, while the attribute *achirality* is concerned with self-enantiomeric relationships to result in achiral promolecules (cf. Figs. 1, 2). The attribute *RS-stereogenicity* is concerned with *RS*-diastereomeric relationships, while the attribute *RS-astereogenicity* is concerned with self-*RS*-diastereomeric relationships to give *RS*-astereogenic promolecules. The attribute *sclerality* is concerned with holantimeric relationships, while the attribute *asclerality* is concerned with self-holantimeric relationships to give ascleral promolecules. The three pairs of attributes are combined to generate five types of stereoisograms (or five types of quadruplets of *RS*-stereoisomers) as categorized in Fig. 3.

By the formulation of stereoisograms, the term *absolute configuration* is concluded to exhibit three aspects:

1. Chiral aspect: The chiral aspect of the term *absolute configuration* is generated by reflection operations and corresponds to enantiomeric relationships, each of which is concerned with the appearance of a pair of enantiomers.
2. *RS*-Stereogenic aspect: The *RS*-stereogenic aspect of the term *absolute configuration* is generated by *RS*-permutation operations and corresponds to *RS*-diastereomeric relationships, each of which is concerned with the appearance of a pair of *RS*-diastereomers. The *RS*-diastereomers of each pair are differentiated by the *RS*-stereodescriptors due to the CIP system.
3. Scleral aspect: The scleral aspect of the term *absolute configuration* is generated by ligand-reflection operations and corresponds to holantimeric relationships, each of which is concerned with the appearance of a pair of holantimers.

It follows that the term *absolute configuration* is determined by examining properties of a quadruplet of *RS*-stereoisomers, which belongs to one of the five types of stereoisograms.

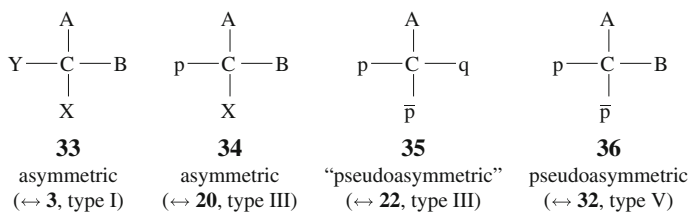
### 2.3.2 Asymmetric centers and pseudoasymmetric centers

Asymmetric centers due to the criterion of van't Hoff [33] are based on *RS*-permutational conversions of a squareplanar graph with four vertices, as exemplified by **33** in Fig. 4 (cf. page 2). Note that, mathematically speaking, the four vertices of a squareplanar graph are permuted by the symmetric group of degree 4 ( $S^{[4]}$ ).

	<i>RS</i> -astereogenic	<i>RS</i> -stereogenic
chiral	<p><b>3</b> (<math>[\theta]_{10}</math>) <math>C_2, C_1, I</math></p>	<p><b>4</b> (<math>[\theta]_{28}</math>) <math>C_2, C_1, I</math></p>
	<p><b>5</b> (<math>[\theta]_{20}</math>) <math>T_{\bar{\sigma}}, T, II</math></p> <p><b>6</b> (<math>[\theta]_3</math>) <math>C_{3\bar{\sigma}}, C_3, II</math></p> <p><b>7</b> (<math>[\theta]_{15}</math>) <math>C_{3\bar{\sigma}}, C_3, II</math></p> <p><b>8</b> (<math>[\theta]_{22}</math>) <math>C_{3\bar{\sigma}}, C_3, II</math></p> <p><b>9</b> (<math>[\theta]_{21}</math>) <math>C_{3\bar{\sigma}}, C_3, II</math></p> <p><b>10</b> (<math>[\theta]_5</math>) <math>C_{2\bar{\sigma}}, C_2, II</math></p> <p><b>11</b> (<math>[\theta]_{25}</math>) <math>C_{2\bar{\sigma}}, C_2, II</math></p> <p><b>12</b> (<math>[\theta]_{17}</math>) <math>C_{\bar{\sigma}}, C_1, II</math></p> <p><b>13</b> (<math>[\theta]_9</math>) <math>C_{\bar{\sigma}}, C_1, II</math></p> <p><b>14</b> (<math>[\theta]_{12}</math>) <math>C_{\bar{\sigma}}, C_1, II</math></p> <p><b>15</b> (<math>[\theta]_{16}</math>) <math>C_{\bar{\sigma}}, C_1, II</math></p> <p><b>16</b> (<math>[\theta]_{17}</math>) <math>C_{\bar{\sigma}}, C_1, II</math></p> <p><b>17</b> (<math>[\theta]_{24}</math>) <math>C_{\bar{\sigma}}, C_1, II</math></p> <p><b>18</b> (<math>[\theta]_{26}</math>) <math>C_{\bar{\sigma}}, C_1, II</math></p> <p><b>19</b> (<math>[\theta]_{27}</math>) <math>C_{\bar{\sigma}}, C_1, II</math></p>	<p><b>20</b> (<math>[\theta]_{11}</math>) <math>C_1, C_1, III</math></p> <p><b>21</b> (<math>[\theta]_{14}</math>) <math>C_1, C_1, III</math></p> <p><b>22</b> (<math>[\theta]_{18}</math>) <math>C_1, C_1, III</math></p> <p><b>23</b> (<math>[\theta]_{19}</math>) <math>C_1, C_1, III</math></p> <p><b>24</b> (<math>[\theta]_{29}</math>) <math>C_1, C_1, III</math></p> <p><b>25</b> (<math>[\theta]_{30}</math>) <math>C_1, C_1, III</math></p>
achiral	<p><b>26</b> (<math>[\theta]_{11}</math>) <math>T_{d\bar{\sigma}}, T_d, IV</math></p> <p><b>27</b> (<math>[\theta]_{12}</math>) <math>C_{3v\bar{\sigma}}, C_{3v}, IV</math></p> <p><b>28</b> (<math>[\theta]_{14}</math>) <math>C_{2v\bar{\sigma}}, C_{2v}, IV</math></p> <p><b>29</b> (<math>[\theta]_{23}</math>) <math>S_{4\bar{\sigma}\bar{\sigma}}, S_4, IV</math></p> <p><b>30</b> (<math>[\theta]_6</math>) <math>C_{s\bar{\sigma}}, C_s, IV</math></p> <p><b>31</b> (<math>[\theta]_8</math>) <math>C_{s\bar{\sigma}\bar{\sigma}}, C_s, IV</math></p>	<p><b>32</b> (<math>[\theta]_{13}</math>) <math>C_s, C_s, V</math></p>

**Fig. 3** Quadruplets of *RS*-Stereoisomers (Types I to V) for tetrahedral promolecules. The symbols *A*, *B*, *X*, and *Y* represent atoms or achiral ligands. The symbols *p*, *q*, *r*, and *s* represents chiral ligands, while each symbol with an *overbar* represents the corresponding chiral ligand with the opposite chirality sense. An arbitrary promolecule is depicted as a representative of each quadruplet of *RS*-stereoisomers. The compound number (its partition), its *RS*-stereoisomeric group, its point group, and its stereoisogram type are attached to each promolecule. Representative promolecules in *gray boxes* exhibit chirality unfaithfulness





**Fig. 4** Asymmetric and pseudoasymmetric centers of squareplanar graphs governed by the symmetric group of degree 4 ( $S^{[4]}$ )

The center of **34** is also categorized to be asymmetric by obeying the criterion of van't Hoff. The center of **36** is asymmetric, but later referred to as being pseudoasymmetric, because **36** corresponds to such an achiral entity as **32**. The center of **35** is asymmetric, but referred to as being “pseudoasymmetric” in a similar way to **36**, although **35** corresponds to such a chiral entity as **22**.

As found in Fig. 4, the term *asymmetric centers* due to van't Hoff may refer to chiral or achiral entities, where the coinage of the term *pseudoasymmetric centers* is an apparent remedy to conceal the inconsistency. The terms *asymmetric centers* and *pseudoasymmetric centers* should be used in historical contexts concerning the criterion due to van't Hoff and his successors as implied by the graphs listed in Fig. 4.

### 2.3.3 Chirality faithfulness in place of “reflection-invariance”

Lowercase *rs*-descriptors are derived from the *RS*-descriptors in the CIP system to specify **35** (or **22**) as well as **36** (or **32**), where the changing from the uppercase letters (*RS*) into the lowercase letters (*rs*) is ascribed to the reflection-invariance of assigned results [3, page 32]. The coinage of the expression *reflection-invariant descriptors* has aimed at categorizing **35** and **36** into a single category for the purpose of arguing against a criticism [31].

Strictly speaking, the coinage of “reflection-invariant” suffers from the methodology based on a single pair of attributes (chirality/achirality), where pairing between enantiomers is solely considered to be permitted. The same descriptor *r* (a reflection-invariant descriptor) is assigned to each of an enantiomeric pair (e.g., **35** (or **22**) and its enantiomer), while the reflection-invariant descriptor for **36** (or **32**) is concerned with a single achiral entity. Thus, reflection-invariant descriptors are treated as exceptional cases, because pairing between *R* and *S* (or between *r* and *s*) is presumed to refer to a pair of enantiomers in the conventional stereochemistry (and the CIP system).

In contrast, the stereoisogram approach stems from the three pairs of attributes, where the *RS*-descriptors are assigned to a pair of *RS*-diastereomers (not to a pair of enantiomers) by considering the pair of *RS*-stereogenicity/*RS*-astereogenicity (not by considering the pair of chirality/achirality). It is important to examine whether or not *RS*-descriptors due to *RS*-stereogenicity is faithful to the chiral aspect of absolute configuration. Hence, the term *chirality faithfulness* has been coined in place of the term “reflection-invariant” [13]. A more rational methodology can be formulated by considering the scleral aspect of absolute configuration as described in the following paragraphs.

Let us consider the priority sequence  $A(1) > B(2) > X(3) > Y(4)$ , where A, B, X, and Y are achiral proligands in isolation and the sequential numbers 1–4 represent their priorities. Then the priority sequence is converted into  $A(\bar{1}) > B(\bar{2}) > X(\bar{3}) > Y(\bar{4})$  by a reflection operation. This conversion can be expressed by the following permutation called a *priority permutation*:

$$\begin{pmatrix} 1 & 2 & 3 & 4 \\ \bar{1} & \bar{2} & \bar{3} & \bar{4} \end{pmatrix} = \overline{(1)(2)(3)(4)}, \quad (1)$$

which exhibits a zero swap (no permutation as one of even permutations). This priority permutation is referred to as being *chirality-faithful*.

Suppose that the position numbering of a skeleton is selected to be identical with the priority sequence, as found **1** (Figs. 1 or 2). When a set of proligands A, B, X, and Y is placed to give the priority sequence  $A(1) > B(2) > X(3) > Y(4)$ , the *R*-stereodescriptor is assigned to **1**. Because the priority permutation is chirality-faithful, the *R*-stereodescriptor is assigned to its holantimer **2** (cf.  $A(\bar{1}) > B(\bar{2}) > X(\bar{3}) > Y(\bar{4})$ ).

Let us consider the priority sequence  $p(1) > \bar{p}(2) > q(3) > \bar{q}(4)$ , where  $p/\bar{p}$  and  $q/\bar{q}$  are two pairs of enantiomeric proligands in isolation and the sequential numbers 1–4 represent their priorities. Then the priority sequence is converted into  $p(\bar{2}) > \bar{p}(\bar{1}) > q(\bar{4}) > \bar{q}(\bar{3})$  by a reflection operation. This conversion can be expressed by the following priority permutation:

$$\begin{pmatrix} 1 & 2 & 3 & 4 \\ \bar{2} & \bar{1} & \bar{4} & \bar{3} \end{pmatrix} = \overline{(1\ 2)(3\ 4)}, \quad (2)$$

which exhibits two swaps (an even permutation). This priority permutation is also referred to as being *chirality-faithful*.

When a set of proligands  $p$ ,  $\bar{p}$ ,  $q$ , and  $\bar{q}$  is placed on the four vertices of **1** (Figs. 1 or 2) so as to give the priority sequence  $p(1) > \bar{p}(2) > q(3) > \bar{q}(4)$ . Then, the *R*-stereodescriptor is assigned to **1**. Because the priority permutation is chirality-faithful, the *R*-stereodescriptor is assigned to its holantimer **2** (cf.  $p(\bar{2}) > \bar{p}(\bar{1}) > q(\bar{4}) > \bar{q}(\bar{3})$ ).

As exemplified by Eqs. (1) and (2), we obtain the following definition of chirality faithfulness, which casts a renewed light on the previous discussion [13].

**Definition 1** (Chirality-faithful absolute configurations) An even priority permutation is chirality-faithful, so that the holantimers of the corresponding pair are characterized by the same stereodescriptor.

On the other hand, let us consider the priority sequence  $A(1) > B(2) > p(3) > \bar{p}(4)$ , where the sequential numbers 1–4 represent their priorities. Then the priority sequence is converted into  $A(\bar{1}) > B(\bar{2}) > p(\bar{4}) > \bar{p}(\bar{3})$  by a reflection operation. This conversion can be expressed by the following priority permutation:

$$\begin{pmatrix} 1 & 2 & 3 & 4 \\ \bar{1} & \bar{2} & \bar{4} & \bar{3} \end{pmatrix} = \overline{(1)(2)(3\ 4)}, \quad (3)$$

which exhibits one swap (odd permutation). Such an odd priority permutation is referred to as being chirality-unfaithful.

When a set of proligands A, B, p, and  $\bar{p}$  is placed on the vertices of **1** (Figs. 1 or 2), so that the priority sequence  $A(1) > B(2) > p(3) > \bar{p}(4)$  assigns the *R*-stereodescriptor to **1**. Because the priority permutation is chirality-unfaithful, the *S*-stereodescriptor is assigned to its holantimer  $\bar{\mathbf{2}}$  (cf.  $A(\bar{1}) > B(\bar{2}) > p(\bar{4}) > \bar{p}(\bar{3})$ ).

As exemplified by Eq. (3), we obtain the following definition of chirality unfaithfulness:

**Definition 2** (*Chirality-unfaithful absolute configurations*) An odd priority permutation is chirality-unfaithful, so that the holantimers of the corresponding pair are characterized by opposite stereodescriptors.

Chirality faithfulness and unfaithfulness defined by Definitions 1 and 2 influence configurational notations for characterizing a quadruplet of promolecules contained in a stereoisogram. Thus, a halantimeric relationship characterized by the same stereodescriptor (due to chirality faithfulness of Definition 1) results in an enantiomeric relationship characterized by opposite stereodescriptors, which have been referred to as ‘reflection-variant stereodescriptors’ [3, page 32]. Another halantimeric relationship characterized by opposite stereodescriptors (due to chirality unfaithfulness of Definition 2) results in an enantiomeric relationship characterized by the same stereodescriptor, which has been referred to as ‘a reflection-invariant stereodescriptor’ [3, page 32].

It should be noted that the concept of chirality faithfulness (Definition 1) or chirality unfaithfulness (Definition 2) is concerned with a quadruplet of promolecules contained in a stereoisogram. Thereby, the three aspects of absolute configurations are evenly taken into consideration. As a result, such expressions as ‘chirality-faithful stereoisograms’ and ‘chirality-faithful quadruplets’ are permissible.

In contrast, the term ‘reflection-invariant’ is concerned only with a pair of enantiomers due to chirality. In other words, it overlooks *RS*-diastereomeric relationships (due to *RS*-stereogenicity) and holantimeric relationships (due to sclerality).

### 2.3.4 *RS*-stereoisomeric centers

Chiral centers and stereogenic centers, which have been discussed in page 2, have been based on a single pair of attributes (chirality/achirality) in the conventional stereochemistry. Hence, their scopes are not fully separated so as to provide the stereochemical terminology with confusion, as described in page 2.

In the stereoisogram approach, on the other hand, the center atom of the reference promolecule of a stereoisogram is called an *RS*-stereoisomeric center, which is correlated to the three aspects of absolute configuration.

1. When we focus our attention on chirality, the chiral aspect of an *RS*-stereoisomeric center is referred to as a *chirality center*. It should be noted that the central atom of each type-II promolecule (**5–19** in Fig. 3) is a chirality center, although the corresponding pair of enantiomers is not characterized by *RS*-stereodescriptors of the CIP system.

2. When we focus our attention on *RS*-stereogenicity, the *RS*-stereogenic aspect of an *RS*-stereoisomeric center is referred to as an *RS-stereogenic center*. In this context, the *RS*-stereodescriptors due to the CIP system are concerned with *RS*-stereogenic centers, not with chirality centers. Note that the central atom of a type-V promolecule (**32** in Fig. 3) is characterized by the *RS*-stereodescriptors due to the CIP system, because it is regarded as an *RS*-stereogenic center, not as a chirality center.
3. When we focus our attention on sclerality, the scleral aspect of an *RS*-stereoisomeric center is referred to as a *sclerality center*.

It should be emphasized that chirality centers, *RS*-stereogenic centers, and sclerality centers represent independent concepts, so that they can coexist according to the five types of stereoisograms. This means that enantiomeric relationships due to chirality centers can coexist with *RS*-diastereomeric relationships due to *RS*-stereogenic centers, even though the conventional stereochemistry insists on the dichotomy between enantiomers and diastereomers.

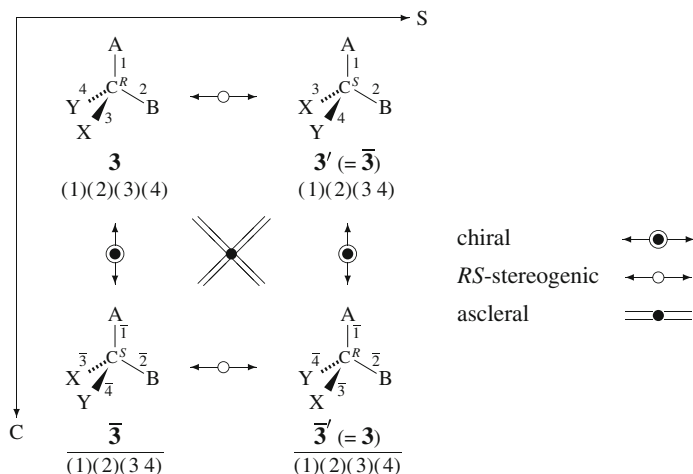
### 3 *RS*-stereogenicity to assign *RS*-stereodescriptors

As discussed above, *RS*-stereodescriptors of the CIP system are concerned with the *RS*-stereogenic aspects of absolute configurations, which characterize quadruplets contained in stereoisograms. Because stereoisograms of types I, III, and V exhibit *RS*-stereogenicity, they are characterized by *RS*-stereodescriptors. Such *RS*-stereodescriptors as used originally to determine *RS*-stereogenic aspects are appropriated to characterize chiral aspects, where the concept of chirality faithfulness is important to discuss the scope and limitations of *RS*-stereodescriptors.

#### 3.1 Chirality-faithful *RS*-stereodescriptors for type-I stereoisograms

*RS*-Stereodescriptors of the CIP system are originally aimed at differentiating two entities of an enantiomeric pair [30]. Although permutations (not restricted to *RS*-permutations) and reflections are differentiated, two tetrahedral entities with the constitution ABXY which are differentiated by a permutation have been recognized as being enantiomeric in the conventional stereochemistry [3, page 14]. It follows that the relationship due to a permutation operation is mixed up with the enantiomeric relationship due to a reflection operation, because both the operations provide the same result. However, the equality between  $\bar{\mathbf{1}}$  and  $\mathbf{2}$  does not mean the equalization between the permutation operation and the reflection operation.

According to the stereoisogram approach, permutation operations are first restricted to *RS*-permutations, which correspond to reflections but maintain the chirality senses of permuted proligands in isolation (i.e., under detached conditions). Then, *RS*-permutations and reflections are integrated to generate an *RS*-stereoisomeric group, e.g.,  $\mathbf{T}_{d\sigma\bar{1}}$  for a tetrahedral skeleton. For example, the promolecule (**3**) with the constitution ABXY ( $[\theta]_{10} = [1, 1, 1, 1; 0, 0, 0, 0, 0, 0, 0]$ ) is characterized by a type-I stereoisogram shown in Fig. 5. The reference promolecule **3** belongs to the *RS*-



**Fig. 5** Stereoisogram of type I in which the reference promolecule **3** belongs to the *RS*-stereoisomeric group  $C_{\hat{T}}$ . The reference promolecule **3** belongs to the point group  $C_1$ . A stereoisogram of type I is chirality-faithful, so that the same *R*-descriptor is assigned to the reference promolecule **3** and its holantimer  $\bar{3}' (= \bar{3})$

stereoisomeric group  $C_{\hat{T}}$ , which is a subgroup of  $T_{d\bar{\sigma}\hat{T}}$  [23]:

$$C_{\hat{T}} = \{I, \hat{T}\} \sim \{(1)(2)(3)(4), \overline{(1)(2)(3)(4)}\}. \quad (4)$$

This means that the *RS*-stereoisomeric group  $C_{\hat{T}}$  fixes the reference promolecule **3** under the action of the *RS*-stereoisomeric group  $T_{d\bar{\sigma}\hat{T}}$ . Note that the quadruplet (a pair of **3** and  $\bar{3}$  and a duplicated pair of  $\bar{3}'$  and  $\bar{3}$ ) shown in Fig. 5 is counted once under the action of  $T_{d\bar{\sigma}\hat{T}}$ , where two enantiomeric pairs coincide with each other.

From the viewpoint of point groups, on the other hand, the reference promolecule **3** belongs to the point group  $C_1 (= \{I\} \sim \{(1)(2)(3)(4)\})$ . This means that the point group  $C_1$  fixes the reference promolecule **3** under the action of the point group  $T_d$ . Note that the enantiomeric pair (**3** and  $\bar{3}$ ) shown in Fig. 5 is counted once under the action of  $T_d$ .

The 6th row of Table 1 indicates the following subduction:

$$T_{d\bar{\sigma}\hat{T}}(/C_{3v\bar{\sigma}\hat{T}}) \downarrow C_{\hat{T}} = 4C_{\hat{T}}(/C_{\hat{T}}), \quad (5)$$

which shows the original four-membered orbit is divided into four one-membered  $C_{\hat{T}}(/C_{\hat{T}})$ -orbits. Each of the four achiral proligands (A, B, X, and Y) occupies a one-membered  $C_{\hat{T}}(/C_{\hat{T}})$ -orbit, which is determined to be homospheric [23, 24].

From the viewpoint of point groups, on the other hand, the generation of the reference promolecule **3** corresponds to the following subduction:

$$T_d(/C_{3v}) \downarrow C_1 = 4C_1(/C_1) \quad (6)$$

which shows the original four-membered orbit is divided into four one-membered  $C_1(/C_1)$ -orbits. Each of the four achiral proligands (A, B, X, and Y) occupies a one-membered  $C_1(/C_1)$ -orbit, which is determined to be hemispheric [20]. Note that a chiral proligand can also occupies a one-membered  $C_1(/C_1)$ -orbit to give the  $C_1$ -molecule.

According to the stereoisogram approach, the type-I stereoisogram shown in Fig. 5 exhibits ascleral properties, which result in the coalescence of the enantiomeric relationship with the *RS*-diastereomeric relationship. In other words, chirality for the enantiomeric pair of **3** and  $\bar{\mathbf{3}}$  and *RS*-stereogenicity for the *RS*-diastereomeric pair of **3** and  $\mathbf{3}' (= \bar{\mathbf{3}})$  are distinct concepts, but the two kinds of pairs coalesce with each other. This standpoint is different from the conventional methodology which pays attention to chirality but overlooks *RS*-stereogenicity in terms of the dichotomy between enantiomers and diastereomers.

As discussed for Definitions 1 and 2, the stereoisogram approach throws a different light on the *RS*-stereodescriptors of the CIP system. The priority sequence  $A > B > X > Y$  (A, B, X, and Y are achiral proligands in isolation) is applied to an *RS*-diastereomeric pair, i.e., **3** and  $\mathbf{3}' (= \bar{\mathbf{3}})$ , so that *R* is assigned to **3** while *S* is assigned to  $\mathbf{3}' (= \bar{\mathbf{3}})$ . This case is characterized by a even permutation shown in Eq. (1), which is concluded to be chirality-faithful (Definition 1). In other words, the priority sequence  $A > B > X > Y$  is unchanged under a reflection operation. Hence the enantiomeric pair of **3** and  $\bar{\mathbf{3}} (= \mathbf{3}')$  is permitted to be differentiated by *R* and *S*.

As a result, the *RS*-stereodescriptors, which are originally used to determine the *RS*-stereogenic aspect of absolute configuration, are appropriated to characterize the chiral aspect in the quadruplet represented by the type-I stereoisogram shown in Fig. 5. The chirality faithfulness discussed in Definition 1 is concerned with the scleral aspect of absolute configuration, where the type-I stereoisogram (Fig. 5) exhibits self-holantimeric character. Thus the *RS*-stereodescriptors influence the three aspects of absolute configuration through chirality faithfulness.

As the next example of a type-I quadruplet, let us examine a stereoisogram shown in Fig. 6. The reference promolecule **4** ( $p\bar{p}q\bar{q}$ ,  $[\theta]_{28} (= [0, 0, 0, 0; 1, 1, 1, 1, 0, 0, 0, 0])$ ) belongs to the *RS*-stereoisomeric group  $C_{\hat{\sigma}}$ :

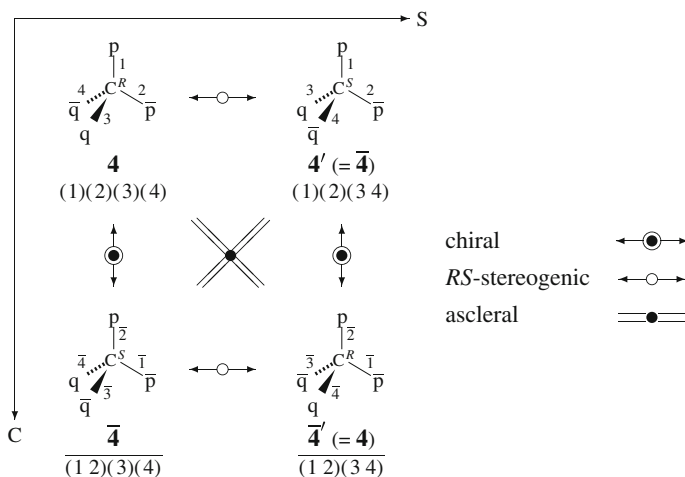
$$C_{\hat{\sigma}} = \{I, \hat{C}_{2(1)}\} \sim \{(1)(2)(3)(4), \overline{(1\ 2)(3\ 4)}\}, \quad (7)$$

which is a subgroup of  $T_{d\hat{\sigma}\hat{I}}$  [23]. This means that the *RS*-stereoisomeric group  $C_{\hat{\sigma}}$  fixes the reference promolecule **4** under the action of the *RS*-stereoisomeric group  $T_{d\hat{\sigma}\hat{I}}$ . Note that the quadruplet (a pair of **4** and  $\bar{\mathbf{4}}$  and a duplicated pair of  $\mathbf{4}'$  and  $\bar{\mathbf{4}}'$ ) shown in Fig. 6 is counted once under the action of  $T_{d\hat{\sigma}\hat{I}}$ , where two enantiomeric pairs coincide with each other.

The 4th row of Table 1 indicates the following subduction:

$$T_{d\hat{\sigma}\hat{I}}(/C_{3v\hat{\sigma}\hat{I}}) \downarrow C_{\hat{\sigma}} = 2C_{\hat{\sigma}}(/C_1), \quad (8)$$

which shows the original four-membered orbit is divided into two two-membered  $C_{\hat{\sigma}}(/C_1)$ -orbits. A pair of enantiomeric proligands (*p* and  $\bar{p}$ ) in isolation occupies a



**Fig. 6** Stereoisogram of type I which belongs to the  $RS$ -stereoisomeric group  $C_{\overline{\sigma}}$ . The group  $C_{\overline{\sigma}}$  is considered to be a subgroup of  $C_{S\overline{\sigma}}$ , where **4** is fixed under the action of  $C_{\overline{\sigma}}$ . The reference promolecule **4** belongs to the point group  $C_1$ . A stereoisogram of type I is chirality-faithful, so that the same  $R$ -descriptor is assigned to the reference promolecule **4** and its holantimer  $\overline{4}' (= \overline{4})$

two-membered  $C_{\overline{\sigma}}(C_1)$ -orbit (positions 1 and 2), which is determined to be enantiospheric [23,24]. Another pair of enantiomeric proligands ( $q$  and  $\overline{q}$ ) in isolation occupies another two-membered  $C_{\overline{\sigma}}(C_1)$ -orbit (positions 3 and 4), which is also determined to be enantiospheric [23,24]. These modes of occupation generate the reference promolecule **4**.

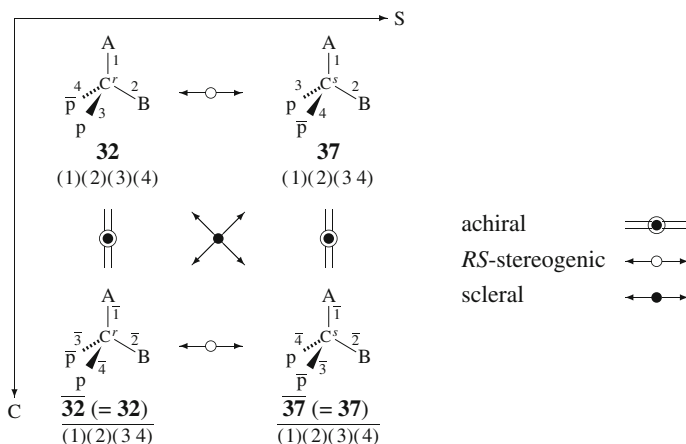
From the viewpoint of point groups, on the other hand, the generation of the reference promolecule **4** corresponds to the subduction represented by Eq. (6). Each of the four achiral proligands ( $p$ ,  $\overline{p}$ ,  $q$ , and  $\overline{q}$ ) occupies a one-membered  $C_1(C_1)$ -orbit, which is determined to be hemispheric [20].

The type-I stereoisogram shown in Fig. 6 can be discussed in a similar way to the type-I stereoisogram shown in Fig. 5. Chirality for the enantiomeric pair of **4** and  $\overline{4}$  and  $RS$ -stereogenicity for the  $RS$ -diastereomeric pair of **4** and  $\overline{4}' (= \overline{4})$  are distinct concepts, but the two kinds of pairs coalesce with each other.

The priority sequence  $p > \overline{p} > q > \overline{q}$  is applied to an  $RS$ -diastereomeric pair, i.e., **4** and  $\overline{4}' (= \overline{4})$ , so that  $R$  is assigned to **4** while  $S$  is assigned to  $\overline{4}' (= \overline{4})$ . This case is characterized by an even permutation shown in Eq. (2), which is concluded to be chirality-faithful (Definition 1). It follows that the  $RS$ -stereodescriptors, which are originally used to determine the  $RS$ -stereogenic aspect, are appropriated to characterize the chiral aspect of absolute configuration. Hence, the enantiomeric pair of **4** and  $\overline{4}$  is permitted to be differentiated by the  $RS$ -stereodescriptors of the CIP system, which are originally used to determine the  $RS$ -stereogenic aspect of absolute configuration.

### 3.2 Chirality-unfaithful $RS$ -stereodescriptors for type-V stereoisograms

The promolecule **32** (Fig. 3,  $ABp\overline{p}$ ,  $[\theta]_{13} = [1, 1, 0, 0; 1, 1, 0, 0, 0, 0, 0, 0, 0]$ ) belongs to the  $RS$ -stereoisomeric group  $C_S$ :



**Fig. 7** Stereoisogram of type V in which the reference promolecule **32** belongs to the *RS*-stereoisomeric group  $C_s$ . The reference promolecule **32** belongs to the point group  $C_s$ . A stereoisogram of type V is chirality-unfaithful, so that an *r*-descriptor is assigned to the reference promolecule **32**, while an *s*-descriptor is assigned to its holantimer **37** ( $= 37$ )

$$C_s = \{I, \sigma_d(2)\} \sim \{(1)(2)(3)(4), \overline{(1)(2)(34)}\}, \tag{9}$$

which is a subgroup of  $T_{d\bar{\sigma}\hat{I}}$  [23]. Note that the group  $C_s$  can be regarded as a point group, because it is also a subgroup of the point group  $T_d$ . The corresponding stereoisogram of type V is shown in Fig. 7, which exhibits pseudoasymmetry.

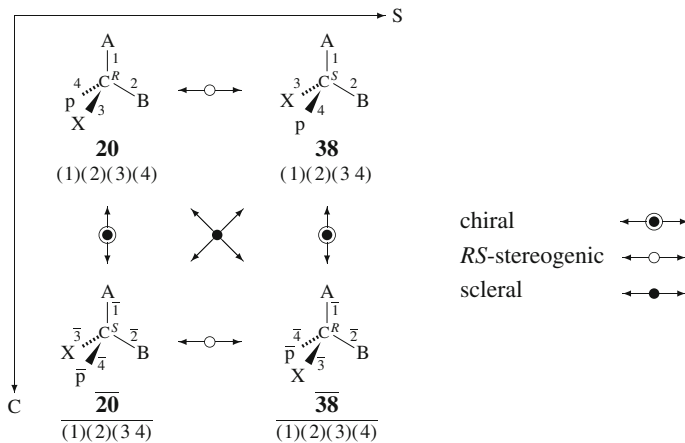
The 5th row of Table 1 indicates the following subduction:

$$T_{d\bar{\sigma}\hat{I}}(/C_{3v\bar{\sigma}\hat{I}}) \downarrow C_s = C_s(/C_1) + 2C_s(/C_s), \tag{10}$$

which shows the original four-membered orbit is divided into one two-membered  $C_s(/C_1)$ -orbit and two one-membered  $C_s(/C_s)$ -orbits. A pair of enantiomeric proligands (*p* and  $\bar{p}$ ) in isolation occupies the two-membered  $C_s(/C_1)$ -orbit (positions 3 and 4), which is determined to be enantiospheric [23,24]. An achiral proligand (*A* or *B*) occupies each one-membered  $C_s(/C_s)$ -orbit (position 1 or position 2), which is determined to be homospheric [23,24]. These modes of occupation generate the reference promolecule **32**. The identical mode of occupation can be obtained from the viewpoint of point groups.

According to the stereoisogram approach, the type-V stereoisogram shown in Fig. 7 exhibits achiral properties, which result in self-enantiomeric relationships (the vertical equality symbols). The *RS*-stereogenicity for the *RS*-diastereomeric pair of **32** and **37** is a distinct concept from achirality for **32** or **37**. This standpoint is different from the conventional methodology which uses the term ‘stereogenicity’ (or ‘pseudoasymmetry’) to explain the situations of **32** and **37**. Note that the concept of ‘stereogenicity’ is correlated to a diastereomeric relationship, which is incapable of generating equivalence classes (See Footnote 1). In contrast, the concept of *RS*-stereogenicity is correlated to an *RS*-diastereomeric relationship, which is capable of generating equivalence classes.





**Fig. 8** Chirality-faithful stereoisogram of type III in which the reference promolecule **20** belongs to the *RS*-stereoisomeric group  $C_1$ . The reference promolecule **20** belongs to the point group  $C_1$ . This stereoisogram of type III is chirality-faithful, so that the same *R*-descriptor is assigned to the reference promolecule **20** and its holantimer **38**

The priority sequence  $A(1) > B(2) > p(3) > \bar{p}(4)$  obeys an odd permutation during reflection (cf. Eq. (3)), so that it is concluded to be chirality-unfaithful (Definition 2). Hence, the lowercase *r*-descriptor is assigned to the reference promolecule **32**, while the lowercase *s*-descriptor is assigned to its *RS*-diastereomer **37**. They are paired in terms of the *RS*-diastereomeric relationship (the horizontal double-headed arrow), but not in terms of an enantiomeric relationship.

### 3.3 Chirality faithfulness for type-III stereoisograms

Type-I stereoisograms are always chirality-faithful and type-V stereoisograms are always chirality-unfaithful. In contrast, type-III stereoisograms may be chirality-faithful or chirality-unfaithful, dependent upon the priority sequences of proligands.

#### 3.3.1 Chirality-faithful *RS*-stereodescriptors for type-III stereoisograms

The reference promolecule **20** (Fig. 3, ABXp,  $[\theta]_{11} = [1, 1, 1, 0; 1, 0, 0, 0, 0, 0, 0, 0]$ ), which belongs to the *RS*-stereoisomeric group  $C_1 (= \{I\})$ , generates a type-III stereoisogram shown in Fig. 8. The group  $C_1$  is a subgroup of  $T_{d\bar{\sigma}\hat{I}}$  and a subgroup of the point group  $T_d$  [23].

The first row of Table 1 indicates the following subduction:

$$T_{d\bar{\sigma}\hat{I}}(/C_{3v\bar{\sigma}\hat{I}}) \downarrow C_1 = 4C_1(/C_1), \quad (11)$$

which shows the original four-membered orbit is divided into four one-membered  $C_1(/C_1)$ -orbits. The division is also provided from the viewpoint of point groups. Each

of the four achiral proligands (A, B, X, and p) occupies a one-membered  $C_1(/C_1)$ -orbit, which is determined to be hemispheric [23,24].

According to the stereoisogram approach, the type-III stereoisogram shown in Fig. 8 exhibits chiral, *RS*-stereogenic, and scleral properties. The chirality is concerned with the enantiomeric relationship between **20** and  $\overline{\mathbf{20}}$  or between **38** and  $\overline{\mathbf{38}}$  (along the vertical direction). The *RS*-stereogenicity is concerned with the *RS*-diastereomeric relationship between **20** and **38** or between  $\overline{\mathbf{20}}$  and  $\overline{\mathbf{38}}$  (along the horizontal direction). The sclerality is concerned with the holantimeric relationship between **20** and  $\overline{\mathbf{38}}$  or between  $\overline{\mathbf{38}}$  and  $\overline{\mathbf{20}}$  (along the diagonal direction).

The priority sequence  $A(1) > B(2) > X(3) > p(4)$  is converted into  $A(\overline{1}) > B(\overline{2}) > X(\overline{3}) > \overline{p}(\overline{4})$  by a reflection operation. This conversion can be expressed by a priority permutation shown in Eq. (1), which is chirality-faithful according to Definition 1. Because of the chirality faithfulness, the *R*-stereodescriptor is assigned to the reference promolecule **20** as well as to its holantimer  $\overline{\mathbf{38}}$ . As a result, the *S*-stereodescriptor is assigned to its enantiomer  $\overline{\mathbf{20}}$ . Thus, the *RS*-stereodescriptors, which are originally used to determine the *RS*-stereogenic aspect of absolute configuration, are appropriated to characterize the chiral aspect in the quadruplet represented by the type-III stereoisogram shown in Fig. 8.

Among the type-III promolecules listed in Fig. 3, the promolecules without shadowing (i.e., **20**, **21**, **23**, and **25**) generate respective type-III stereoisograms, which exhibit chirality faithfulness.

### 3.3.2 Chirality-unfaithful *RS*-stereodescriptors for type-III stereoisograms

The reference promolecule **22** (Fig. 3,  $Ap\overline{p}q$ ,  $[\theta]_{18} = [1, 0, 0, 0; 1, 1, 1, 0, 0, 0, 0, 0]$ ), which belongs to the *RS*-stereoisomeric group  $C_1 (= \{I\})$ , generates a type-III stereoisogram shown in Fig. 9. The group  $C_1$  is a subgroup of  $T_{d\overline{\sigma}\hat{\tau}}$  and a subgroup of the point group  $T_d$  [23].

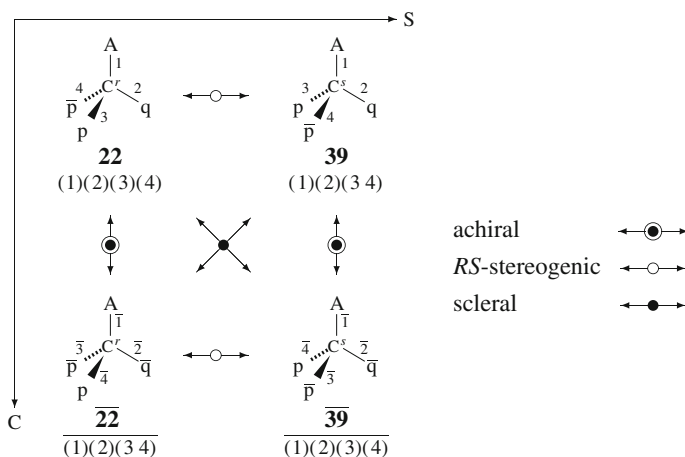
The subduction of Eq. (11) due to the first row of Table 1 indicates that the original four-membered orbit is divided into four one-membered  $C_1(/C_1)$ -orbits. Each of the four achiral proligands (A, p,  $\overline{p}$ , q) occupies a one-membered  $C_1(/C_1)$ -orbit, which is determined to be hemispheric [23,24].

According to the stereoisogram approach, the type-III stereoisogram shown in Fig. 9 can be discussed in a parallel way to Fig. 8, where there appear chirality for enantiomeric relationships (along the vertical direction), *RS*-stereogenicity for *RS*-diastereomeric relationships (along the horizontal direction), and sclerality for holantimeric relationships (along the diagonal direction).

The priority sequence  $A(1) > p(2) > \overline{p}(3) > q(4)$  is converted into  $A(\overline{1}) > \overline{p}(\overline{3}) > \overline{p}(\overline{2}) > \overline{q}(\overline{4})$  by a reflection operation. This conversion can be expressed by an odd priority permutation:

$$\begin{pmatrix} 1 & 2 & 3 & 4 \\ \overline{1} & \overline{3} & \overline{2} & \overline{4} \end{pmatrix} = \overline{(1)(2\ 3)(4)}, \quad (12)$$

which is chirality-unfaithful according to Definition 2. Because of the chirality unfaithfulness, the *r*-stereodescriptor is assigned to the reference promolecule **22** while the *s*-stereodescriptor is assigned to its holantimer  $\overline{\mathbf{39}}$ . As a result, the *r*-stereodescriptor



**Fig. 9** Chirality-unfaithful stereoisogram of type III in which the reference promolecule **22** belongs to the  $RS$ -stereoisomeric group  $C_1$ . The reference promolecule **22** belongs to the point group  $C_1$ . This stereoisogram of type III is chirality-unfaithful, so that an  $r$ -descriptor is assigned to the reference promolecule **22**, while an  $s$ -descriptor is assigned to its holantimer **39**

is assigned to its enantiomer  $\overline{\mathbf{22}}$ , so that the same  $r$ -stereodescriptor is assigned to both **22** and  $\overline{\mathbf{22}}$ . Thus, the pair of  $rs$ -stereodescriptors, which is originally used to determine the  $RS$ -stereogenic aspect of absolute configuration, cannot be appropriated to characterize the chiral aspect in the quadruplet represented by the type-III stereoisogram shown in Fig. 9.

Among the type-III promolecules listed in Fig. 3, the shadowed promolecules (**22** and **24**) generate type-III stereoisograms which exhibit chirality unfaithfulness.

## 4 Successive subductions

### 4.1 Type-V into type-III stereoisograms

By subducing Eq. (10) into  $C_1$ , we obtain the following successive subduction:

$$\begin{aligned} (\mathbf{T}_{d\sigma I}/C_{3v\sigma I}) \downarrow C_s \downarrow C_1 &= C_s(/C_1) \downarrow C_1 + 2C_s(/C_s) \downarrow C_1 \\ &= 2C_1(/C_1) + 2C_1(/C_1) \end{aligned} \quad (13)$$

The achiral proligand B accommodated in the  $C_s(/C_s)$ -orbit of **32** (Fig. 7) is replaced by a proligand q which is chiral in isolation. Thereby the  $C_s(/C_s)$ -orbit of **32** is changed into the  $C_1(/C_1)$ -orbit of **22** (Fig. 9) in accord with Eq. (13). This change reduces the point group  $C_s$  (also an  $RS$ -stereoisomeric group) into  $C_1$ , so that the  $C_s(/C_1)$ -orbit of **32** (for accommodating p and  $\bar{p}$ ) is divided into two  $C_1(/C_1)$ -orbits of **22** in accord with Eq. (13). Although each of the two  $C_1(/C_1)$ -orbits of **22** accommodates p or  $\bar{p}$ , the priority sequence  $A(1) > p(2) > \bar{p}(3) > q(4)$  for **22** is chirality-unfaithful, just as the priority sequence  $A(1) > B(2) > p(3) > \bar{p}(4)$  for **32** is chirality-unfaithful, where a pair of p and  $\bar{p}$  occupies the two-membered  $C_s(/C_1)$ -orbit of **32**.

The type-III stereoisogram (Fig. 9) containing **22** is alternatively drawn by starting from the type-I stereoisogram shown in Fig. 6. The corresponding *RS*-diastereomer **39** is derived from the type-I promolecule **4** (Fig. 6), where the  $\bar{q}$  is replaced by A.

By subducing Eq. (8) into  $C_1$ , we obtain the following successive subduction:

$$\begin{aligned} (\mathbf{T}_{d\bar{\sigma}\bar{\tau}}(\mathbf{C}_{3v\bar{\sigma}\bar{\tau}}) \downarrow \mathbf{C}_{\bar{\sigma}}) \downarrow \mathbf{C}_1 &= 2\mathbf{C}_{\bar{\sigma}}(\mathbf{C}_1) \downarrow \mathbf{C}_1 \\ &= 2 \times 2\mathbf{C}_1(\mathbf{C}_1) \end{aligned} \quad (14)$$

One  $\mathbf{C}_{\bar{\sigma}}(\mathbf{C}_1)$ -orbit accommodating a pair of  $q$  and  $\bar{q}$  is divided into two  $\mathbf{C}_1(\mathbf{C}_1)$ -orbits accommodating  $q$  and A, respectively. Thereby, the other  $\mathbf{C}_{\bar{\sigma}}(\mathbf{C}_1)$ -orbit accommodating a pair of  $p$  and  $\bar{p}$  is also divided into two  $\mathbf{C}_1(\mathbf{C}_1)$ -orbits, but still accommodates  $p$  and  $\bar{p}$ . The priority sequence  $p(1) > \bar{p}(2) > q(3) > \bar{q}(4)$  for **4** is chirality-faithful (even priority permutation), while the priority sequence  $A(1) > p(2) > \bar{p}(3) > q(4)$  for **39** (or **22**) is chirality-unfaithful (odd priority permutation).

The derivation of **24** (type III, chirality-unfaithful) from **4** (type I, chirality-faithful) can be discussed in a similar way to the above derivation of **22** (type III, chirality-unfaithful) from **4** (type I, chirality-faithful).

#### 4.2 Type-I into type-III stereoisograms

By subducing Eq. (5) into  $C_1$ , we obtain the following successive subduction:

$$\begin{aligned} (\mathbf{T}_{d\bar{\sigma}\bar{\tau}}(\mathbf{C}_{3v\bar{\sigma}\bar{\tau}}) \downarrow \mathbf{C}_{\bar{\tau}}) \downarrow \mathbf{C}_1 &= 4\mathbf{C}_{\bar{\tau}}(\mathbf{C}_{\bar{\tau}}) \downarrow \mathbf{C}_1 \\ &= 4\mathbf{C}_1(\mathbf{C}_1) \end{aligned} \quad (15)$$

The achiral proligand Y accommodated in the  $\mathbf{C}_{\bar{\tau}}(\mathbf{C}_{\bar{\tau}})$ -orbit of **3** (Fig. 5) is replaced by a chiral proligand p. Thereby the  $\mathbf{C}_{\bar{\tau}}(\mathbf{C}_{\bar{\tau}})$ -orbit of **3** is changed into the  $\mathbf{C}_1(\mathbf{C}_1)$ -orbit of **20** (Fig. 8) in accord with Eq. (15). This change reduces the *RS*-stereoisomeric group  $\mathbf{C}_{\bar{\tau}}$  into  $\mathbf{C}_1$ , so that all of the  $\mathbf{C}_{\bar{\tau}}(\mathbf{C}_{\bar{\tau}})$ -orbits of **3** are subduced into  $\mathbf{C}_1(\mathbf{C}_1)$ -orbits of **20** in accord with Eq. (15). The priority sequence  $A(1) > B(2) > X(3) > p(4)$  for **20** is chirality-faithful, just as the priority sequence  $A(1) > B(2) > X(3) > Y(4)$  for **3** is chirality-faithful.

## 5 Conclusion

Three aspects of absolute configurations, i.e., a chiral aspect, an *RS*-stereogenic aspect, and a scleral aspect, are formulated on the basis of three attributes of a stereoisogram, i.e., chirality, *RS*-stereogenicity, and sclerality. The *RS*-stereodescriptors of the Cahn-Ingold-Prelog (CIP) system are clarified to specify the *RS*-stereogenic aspect, so that they are assigned to a pair of *RS*-diastereomers contained in a type-I, type-III, or type-V stereoisogram. To apply the *RS*-stereodescriptors to the chiral aspect of an absolute configuration, the concept of *chirality faithfulness* is redefined by proposing *odd* and *even priority permutations*.

## References

1. IUPAC Organic Chemistry Division, *Pure Appl. Chem.* **68**, 2193–2222 (1996)
2. IUPAC Chemical Nomenclature and Structure Representation Division, Provisional Recommendations. Nomenclature of Organic Chemistry (2004), [http://www.iupac.org/reports/provisional/abstract04/favre\\_310305.html](http://www.iupac.org/reports/provisional/abstract04/favre_310305.html)
3. G. Helmchen, in “Stereoselective Synthesis”, 4 ed., ed. by G. Helmchen, R.W. Hoffmann, J. Mulzer, E. Schaumann (Georg Thieme, Stuttgart New York, 1996) Vol. 1 of *Methods of Organic Chemistry* (Houben-Weyl). Workbench Edition E21 pp. 1–74
4. E.L. Eliel, S.H. Willen, M.P. Doyle, *Basic organic stereochemistry* (Wiley-Interscience, New York, 2001)
5. S. Fujita, *J. Org. Chem.* **69**, 3158–3165 (2004)
6. S. Fujita, *Tetrahedron* **60**, 11629–11638 (2004)
7. S. Fujita, *J. Math. Chem.* **35**, 265–287 (2004)
8. S. Fujita, *MATCH Commun. Math. Comput. Chem.* **52**, 3–18 (2004)
9. S. Fujita, *J. Chem. Inf. Comput. Sci.* **44**, 1719–1726 (2004)
10. S. Fujita, *MATCH Commun. Math. Comput. Chem.* **53**, 147–159 (2005)
11. S. Fujita, *MATCH Commun. Math. Comput. Chem.* **54**, 39–52 (2005)
12. S. Fujita, *MATCH Commun. Math. Comput. Chem.* **61**, 11–38 (2009)
13. S. Fujita, *J. Comput. Aided Chem.* **10**, 16–29 (2009)
14. S. Fujita, Stereoisograms: A remedy against oversimplified dichotomy between enantiomers and diastereomers in stereochemistry, in *Chemical information and computational challenge in the 21st century*, Chapter 9, ed. by M.V. Putz (Nova, New York, 2012), pp. 223–242
15. S. Fujita, *Tetrahedron* **62**, 691–705 (2006)
16. S. Fujita, Yuki Gosei Kagaku Kyokai-Shi. *J. Synth. Org. Chem. Jpn.* **66**, 995–1004 (2008)
17. S. Fujita, *MATCH Commun. Math. Comput. Chem.* **61**, 39–70 (2009)
18. S. Fujita, *J. Comput. Aided Chem.* **10**, 76–95 (2009)
19. S. Fujita, Prochirality and Pro-RS-stereogenicity. Stereoisogram approach free from the conventional ‘Prochirality’ and ‘Prostereogenicity’, in *Carbon bonding and structures. Advances in physics and chemistry, Vol. 5 of carbon materials: chemistry and physics, Chapter 10*, ed. by M.V. Putz (Springer, Dordrecht, Heidelberg, London, 2011)
20. S. Fujita, *Symmetry and combinatorial enumeration in chemistry* (Springer, Berlin-Heidelberg, 1991)
21. S. Fujita, Diagrammatical approach to molecular symmetry and enumeration of stereoisomers. University of Kragujevac, Faculty of Science, Kragujevac (2007), Vol. 4 of *Mathematical Chemistry Monographs Series*
22. S. Fujita, *Combinatorial Enumeration of Graphs, Three-Dimensional Structures, and Chemical Compounds*, University of Kragujevac, Faculty of Science, Kragujevac (2013), Vol. 15 of *Mathematical Chemistry Monographs Series*
23. S. Fujita, *J. Math. Chem.*, **52**, 508–542 (2014); doi:10.1007/s10910-013-0276-y (2013)
24. S. Fujita, *J. Math. Chem.*, **52**, 543–574 (2014); doi:10.1007/s10910-013-0277-x (2013)
25. K. Mislow, *Introduction to stereochemistry* (Benjamin, New York, 1965)
26. N. North, *Principles and applications of stereochemistry* (Stanley Thornes, Cheltenham, 1998)
27. D.G. Morris, *Stereochemistry* (Royal Society of Chemistry, Cambridge, 2001)
28. S. Fujita, *Tetrahedron* **65**, 1581–1592 (2009)
29. S. Fujita, *MATCH Commun. Math. Comput. Chem.* **61**, 71–115 (2009)
30. R.S. Cahn, C.K. Ingold, V. Prelog, *Angew. Chem. Int. Ed. Eng.* **5**, 385–415 (1966)
31. K. Mislow, J. Siegel, *J. Am. Chem. Soc.* **106**, 3319–3328 (1984)
32. V. Prelog, G. Helmchen, *Angew. Chem. Int. Ed. Eng.* **21**, 567–583 (1982)
33. J.H. van’t Hoff, *Die Lagerung der Atome im Raume* (German Translation by F. Herrmann), Friedrich Vieweg und Sohn, Braunschweig (1877)